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10/019,543	04/09/2002	Satoru Yokomizo	12218/3	1045

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 08/89/04 RA

Office Action Summary	Application No.	Applicant(s)	
	10/019,543	YOKOMIZO ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/28/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A preliminary amendment filed 01/03/2002 is acknowledged and entered. As a result claims 3-15 and 20-21 are amended. It is noted that Applicant states in the accompanying remarks, filed 01/03/2002, that claims 3-7, 9-10, 12-15 and 17 are amended, but the claims' marked-up copy does not correspond with Applicant's remarks.

In addition, there are two sets up claims both filed on 01/03/2002. One set contains claims with multiple dependency, while the other set does not contain any multiple dependency. As applicant indicates a preliminary amendment is being filed to correct multiple dependency, the latter claim set, claims 1-23, is examined and under consideration in this action.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an applications filed in Japan, on 05/19/2000 (Japan 2000-148726), on 12/27/2000 (Japan 2000-396955) and on 01/25/2001 (Japan 2001-16929). It is noted, however, that applicant has not filed a certified copy of the applications as required by 35 U.S.C. 119(b).

Information Disclosure Statement

The information disclosure statement filed 03/26/2002 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it lists a foreign language document indicating a translation has been submitted (i.e. Japan 10-108682), but a translation is not present in the record. The IDS has been placed in the application file, but the above noted information referred

to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Specification

The abstract of the disclosure is objected to because it contains legalese language (e.g. "said gene"). Furthermore, the last sentence in the Abstract contains grammatical errors (e.g. "gene ...is related to synthesize, by an enzyme..."). Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 3, 9-10, 12-13 and 15-16 are objected to because of the following informalities:

Claim 3 recites the term, "P(3HB-co-3HH)" without first properly defining the corresponding meaning (e.g. poly 3-hydroxybutyrate for 3HB). Similarly, the additional claims noted above recite acronyms without properly defining the corresponding meaning (e.g. ALK3, XPR2, ALK1, PHA). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. **Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Base claim 1 recites the phrase "one kind of gene expression cassette" which is vague and indefinite as written. For example, it is unclear if the critical element or characteristic of the cassette is somehow related to the polyester-synthesis associate enzyme gene. The specification indicates that the cassette can of the type with a constitutive promoter or an inducible promoter. However, as written it is unclear how "kind of" is to be interpreted in determining the claim's metes and bounds.

Claims 2 and 3 recite the limitation "the polyester" in referring to claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 7-15 and 19-21 recite the term "derived from" which is vague and indefinite. The term does not appear to be specifically defined in the specification. Regardless, as written, the claims' metes and bounds are indeterminable. For example, "derived from" can be interpreted subjectively to mean a few nucleotides, or in the extreme case a single nucleotide.

Claim 15 is unclear and indefinite as written because it recites that the polyester synthesis-associate gene is PHA synthase or PHA synthase gene and hydratase gene. It is unclear how one gene is concurrently two different genes.

Claim 18 is indefinite as written because it recites that a gene is modified "from at least one gene code CTG to TTA... ". It is unclear how the claim's metes and bounds are to be interpreted in regard to a gene being "from at least one gene code".

The specification indicates that certain yeast species translate the codon – CTG – abnormally and that for this particular codon in such yeast species, the CTG codon can be changed to TTA, etc., so as to properly translate the CTG codon into leucine (Spec. p. 8, bottom ¶; p. 9). However, as written the claim confers ambiguity, because it is unclear how a gene is modified "from...one gene code". Furthermore, the relationship between "gene code" and the subsequent recited codons is unclear as there is no modifier between "gene code" and "CTG" for example. It would be remedial to substitute "codon" for "gene code" and replace the preposition "from" with "in" and include a term such as "wherein" to clarify the relationship between "codon" and "CTG".

In addition, Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: That the codon – CTG – when altered would be limited in the correlative function for encoding a polyester synthesis-associated gene, in an organism that improperly translates said codon, thus producing a non-functional heterologous gene. As written, for example, the claimed gene would have no structure to function correlation in a yeast species that does not abnormally translate the CTG (or CUG) codon.

In addition, base claim 18 recites a "gene". The recited "gene" can be in an *in vitro* environment. However, if it is in an *in vivo* environment, it is unclear what applicants are claiming because the cell would be a part of an organism, i.e. are applicants claiming the gene naturally occurring within any host organism. It would be remedial to include "isolated" before the term "polyester" to clarify the metes and bounds of the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claims 18-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a gene containing modified CTG codons encoding a functional polyester synthesis-associated enzyme gene in the yeast, *Candida maltosa*, does not reasonably provide enablement for modified CTG codons in a polyester synthesis-associated enzyme gene in any organism.**

The test for enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are directed to any polyester synthesis-associated enzyme (PSE) gene with at least one CTG codon replaced by any of the codons, TTA, TTG, CTT, CTC or CTA.. The claims are delimited to encoding a functional enzyme and read on the functionality to be preserved irrespective of the codon substitution. Moreover, the claims are drawn to the modified-codon-gene being functional in any organism.

Nature of the invention. The invention is directed to an altered PSE gene that expresses short polyhydroxyalkanoates forming a polyester polymer.

The only disclosed utility is for the gene to be transformed into a host organism (e.g. yeast) with the aim of polyester polymer production.

State of the art/Unpredictability of the art. It is known that certain specific species of *Candida* read the universally leucine codon CUG as serine. (*See* e.g. Sugiyama et al. Yeast. 1995; 11:43-52). It logically follows, that if one particular species of organism has evolved in such a way, where a specific codon is mistranslated, then if a PSE gene with an altered CTG codon is transformed into an organism that does not mistranslate CTG into something other than leucine, then the gene would not maintain the delimited function of being a PSE gene. For example, under such a scenario, it would be unpredictable if the altered PSE gene would function, without the added burden of undertaking undue experimentation. Indeed, one of skill in the art would not know how to use the invention – the CTG-altered PSE gene in *any* other species.

Amount of guidance provided. There is no significant guidance provided as to using the CTG-altered PSE in other species of organisms, including other yeast genera, or other species of *Candida*.

Number of working examples. The only example provided directed to *C. maltosa*, transformed with the altered PSE gene as represented by SEQ ID NO: 3. (Spec. p. 18, Example 1).

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the

invention, the level of unpredictability in the art and lack of working examples, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-2, 4, 7-15 and 17-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Leaf et al. (Microbiology, 1996; 142:1169-80; see whole document).

The claims are interpreted in light of any ambiguity or indefiniteness noted above. (*Supra*, rejections under § 112, ¶ 2). The limitation polyester synthesis-associated enzyme (PSE) is interpreted broadly to mean virtually any enzyme related in any fashion with polyester synthesis. In addition, claims reciting the term "derived from" when referring to a gene are interpreted as broadly as reasonable to mean a polynucleotide containing even a single nucleotide "derived from" the particularly claimed gene or promoter sequence. With regard to codon usage (i.e. claim 18), first, it is unclear how the claim is to be interpreted, thus any PSE is deemed to read on the claim; second, the claim reads on any naturally occurring gene in any organism, thus based on the frequency of mutation in microorganism, at least some genes occurring naturally would contain a mutated codon.

Leaf et al. teach expressing a bacterial polyhydroxybutyrae synthase in *Saccharomyces cerevisiae*. (e.g. Abstract). More particularly, an expression cassette (pTL85) contains the necessary promoter/terminator elements for expression is *S. cerevisiae*. (e.g. p. 1170, col. 1, under "Methods"; col. 2, under "Plasmid Construction"; p. 1171, col. 2, last ¶ bridging to p. 1172)). Therefore, the expression construct will necessarily contain at least some nucleotides in common with the claimed PSE gene obtained from *Aeromonas caviae*, the particular promoters, as well as terminators. In sum, Leaf et al. anticipates the rejected claims.

4. Claims 1-4, 7-15 and 17-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukui et al. (US 5,981,257; see whole document; hereinafter the '257 patent).

Claim 3 is drawn to the PHA synthase producing 3-hydroxybutyric acid (3HB) and 3-hydroxyhexanoic acid (3HH) wherein the polyester polymer formed is 3HB-co-3HH. Additional claims are interpreted as explained above. (*Supra*, Rejection No. 2)

The '257 patent teaches cells transformed with nucleic acids that comprise a polyester synthase gene wherein the polyester polymer formed comprises 3HB-co-3HH. (e.g. col. 1, ll. 25-55; col. 11, Table 3). Furthermore, the PHA gene is obtained from *Aeromonas caviae*. (e.g. col. 3, l. 32; col. 7, ll. 20-66). The '257 patent explicitly teaches that the host organism, transformed with an expression vector, can be yeast, more particularly *Sacchromyces*. (e.g. col. 4, l. 26). Furthermore, if yeast are to be used as the host organisms, the '257 patent teaches that appropriate expression vectors, such as Yep13 or Ycp50 for example, can be used to provide appropriate promoters/terminators. (e.g. col. 4, l. 47).

Therefore, the expression construct will necessarily share some nucleotides in common with the particular promoters or terminators claimed. In sum, the '257 patent anticipates the rejected claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ray Akhavan/ AU 1636

GERRY LEFFERS
PRIMARY EXAMINER